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DATE: Wednesday, March 03, 2004

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<input type="checkbox"/>	L1	(PASTEURELL\$ OR HAEMOLYT\$ OR HEMOLYTICA\$).ti,ab,clm.	1897
<input type="checkbox"/>	L2	(pasteurell\$ or haemolyt\$ or hemolytica\$).ti,ab,clm.	1897
<input type="checkbox"/>	L3	L2 same (mutant or mutation or mutagenesis or modified or substitution or insertion or deletion or homolog or analog or deleted or delete or insert or modification or aro or aro\$1 or aro-a).ti,ab,clm.	122
<input type="checkbox"/>	L4	L3 and (aro or aroa or aro-a or aromatic\$)	18

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L4: Entry 18 of 18

File: DWPI

Oct 16, 2002

DERWENT-ACC-NO: 1995-224327

DERWENT-WEEK: 200279

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TITLE: Prodn. of attenuated aroA mutants of Pasteurella haemolytica by DNA methylation - useful in vaccines for protection of cattle against P. haemolytica infection

INVENTOR: BRIGGS, R E; TATUM, F M ; BRIGSS, R E

PRIORITY-DATA: 1993US-0162392 (December 6, 1993), 1996US-0643300 (May 8, 1996), 1996US-0643297 (May 8, 1996), 1996US-0643298 (May 8, 1996), 1996US-0643301 (May 8, 1996), 1996US-0643299 (May 8, 1996)

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PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
<input type="checkbox"/>	ES 2173170 T3	October 16, 2002		000	C12N015/74
<input type="checkbox"/>	WO 9516045 A1	June 15, 1995	E	051	C12N015/74
<input type="checkbox"/>	AU 9513031 A	June 27, 1995		000	C12N015/74
<input type="checkbox"/>	EP 733114 A1	September 25, 1996	E	000	C12N015/74
<input type="checkbox"/>	US 5587305 A	December 24, 1996		022	C12N015/09
<input type="checkbox"/>	US 5683900 A	November 4, 1997		022	C12N009/16
<input type="checkbox"/>	US 5693777 A	December 2, 1997		021	C07H021/04
<input type="checkbox"/>	US 5733780 A	March 31, 1998		022	C12N015/74
<input type="checkbox"/>	AU 692817 B	June 18, 1998		000	C12N015/74
<input type="checkbox"/>	US 5824525 A	October 20, 1998		000	C12N001/21
<input type="checkbox"/>	US 5849305 A	December 15, 1998		000	A01J021/00
<input type="checkbox"/>	EP 1149587 A2	October 31, 2001	E	000	A61K039/102
<input type="checkbox"/>	EP 733114 B1	February 27, 2002	E	000	C12N015/74
<input type="checkbox"/>	DE 69430005 E	April 4, 2002		000	C12N015/74

INT-CL (IPC): [A01 J 21/00](#); [A01 J 25/12](#); [A21 C 3/00](#); [A21 C 11/00](#); [A61 K 39/102](#); [C07 H 21/04](#); [C12 N 1/21](#); [C12 N 9/10](#); [C12 N 9/16](#); [C12 N 9/22](#); [C12 N 15/00](#); [C12 N 15/09](#); [C12 N 15/54](#); [C12 N 15/55](#); [C12 N 15/63](#); [C12 N 15/74](#)

ABSTRACTED-PUB-NO: EP 733114B

A method for producing a mutation in a partic. region of DNA of the Pasteurella haemolytica genome comprises: (a) isolating the genomic region; (b) introducing a mutation in the region; (c) methylating the mutated region to prevent endonuclease cleavage at the sites 5'-GATGC-3' or 5'-GCATC-3'; (d) introducing the methylated DNA into P. haemolytica, and (e) screening the transformants for those with the mutation in the region.

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USE - The mutation using methyltransferase allows the construction of defined, attenuated aroA mutants for use as vaccines to protect cattle against P. haemolytica infection.

US 5733780A

A method for producing a mutation in a partic. region of DNA of the Pasteurella haemolytica genome comprises: (a) isolating the genomic region; (b) introducing a mutation in the region; (c) methylating the mutated region to prevent endonuclease cleavage at the sites 5'-GATGC-3' or 5'-GCATC-3'; (d) introducing the methylated DNA into P. haemolytica, and (e) screening the transformants for those with the mutation in the region.

USE - The mutation using methyltransferase allows the construction of defined, attenuated aroA mutants for use as vaccines to protect cattle against P. haemolytica infection.

US 5824525A

A method for producing a mutation in a partic. region of DNA of the Pasteurella haemolytica genome comprises: (a) isolating the genomic region; (b) introducing a mutation in the region; (c) methylating the mutated region to prevent endonuclease cleavage at the sites 5'-GATGC-3' or 5'-GCATC-3'; (d) introducing the methylated DNA into P. haemolytica, and (e) screening the transformants for those with the mutation in the region.

USE - The mutation using methyltransferase allows the construction of defined, attenuated aroA mutants for use as vaccines to protect cattle against P. haemolytica infection.

US 5849305A

A method for producing a mutation in a partic. region of DNA of the Pasteurella haemolytica genome comprises: (a) isolating the genomic region; (b) introducing a mutation in the region; (c) methylating the mutated region to prevent endonuclease cleavage at the sites 5'-GATGC-3' or 5'-GCATC-3'; (d) introducing the methylated DNA into P. haemolytica, and (e) screening the transformants for those with the mutation in the region.

USE - The mutation using methyltransferase allows the construction of defined, attenuated aroA mutants for use as vaccines to protect cattle against P. haemolytica infection.

WO 9516045A

ABSTRACTED-PUB-NO: EP 733114B

EQUIVALENT-ABSTRACTS: A method for producing a mutation in a partic. region of DNA of the Pasteurella haemolytica genome comprises: (a) isolating the genomic region; (b) introducing a mutation in the region; (c) methylating the mutated region to prevent endonuclease cleavage at the sites 5'-GATGC-3' or 5'-GCATC-3'; (d) introducing the methylated DNA into P. haemolytica, and (e) screening the transformants for those with the mutation in the region. USE - The mutation using methyltransferase allows the construction of defined, attenuated aroA mutants for use as vaccines to protect cattle against P. haemolytica infection. US 5587305A A new method for producing a mutation in a particular region of DNA of a P. haemolytica genome comprises: (a) isolating the region of the genome from P. haemolytica; (b) introducing a mutation into the region to form a mutated DNA region; (c) methylating said mutated DNA region with a methylating enzyme which

CHOSEN-DRAWING: Dwg.0/6 Dwg.0/6 Dwg.0/6D Dwg.0/6 Dwg.0/6

First Hit

L4: Entry 1 of 18

File: PGPB

Feb 19, 2004

PGPUB-DOCUMENT-NUMBER: 20040033586
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040033586 A1

TITLE: Attenuated gram negative bacteria

PUBLICATION-DATE: February 19, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Crooke, Helen Rachel	Winnersh Triangle		GB	
Shea, Jacqueline Elizabeth	Winnersh Triangle		GB	
Feldman, Robert Graham	Winnersh Triangle		GB	
Goutebroze, Sylvain Gabriel	Lyon		FR	
Le Gros, Francois-Xavier	Saint Genis Laval		FR	

APPL-NO: 10/ 406686 [PALM]
DATE FILED: April 3, 2003

RELATED-US-APPL-DATA:

Application is a non-provisional-of-provisional application 60/370282, filed April 5, 2002,

INT-CL: [07] C12 N 1/20

US-CL-PUBLISHED: 435/252.3
US-CL-CURRENT: 435/252.3

ABSTRACT:

Disclosed and claimed are a mutant of a gram negative bacterium, wherein said bacterium has at least one mutation in a nucleotide sequence which codes for a polypeptide having an identity which is equal or more than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% with an amino acid sequence coded by a nucleotide sequence selected from the group consisting of nucleotide sequences identified SEQ ID NO: 2, 6, 9, 12, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 75, 78, 81, 84, 87, 90, 93; said mutation resulting in attenuated virulence of the bacterium. Immunogenic compositions and vaccines containing such a mutant are also disclosed and claimed.

RELATED APPLICATIONS/INCORPORATION BY REFERENCE

[0001] This application claims priority from U.S. provisional application Serial No. 60/370,282, filed on Apr. 5, 2002, incorporated herein by reference. The foregoing application, and all documents cited therein or during its prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any

manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

- http://westbrs:9000/bin/cgi-bin/accum_query.pl?MODE=%20%20%20%20Display%20%20%20%... 3/3/04

Oct 20, 1998

**** See image for Certificate of Correction ****

DATE-ISSUED: October 20, 1998

NAME	CITY	STATE	ZIP CODE	COUNTRY
Briggs; Robert E.	Boone	IA		
Tatum; Fred M.	Ames	IA		

CLAIMS:

We claim:

1. A method for producing a mutation in a particular region of DNA of a *P. haemolytica* genome comprising the step of:

isolating said region of the genome from *P. haemolytica*;

introducing a mutation into said region to form a mutated DNA region;

introducing said mutated, DNA region into a *P. haemolytica* cell which does not express a *PhaI* restriction endonuclease, to form transformants; and

screening said transformants for those which have said mutation in said region on chromosomal DNA of said *P. haemolytica* cell.

2. The method of claim 1 wherein said *P. haemolytica* cell which does not express a *PhaI* restriction endonuclease is a natural isolate.

3. The method of claim 1 wherein said *P. haemolytica* cell which does not express a *PhaI* restriction endonuclease is a mutant made by chemical mutagenesis.

4. The method of claim 1 wherein said *P. haemolytica* cell which does not express a *PhaI* restriction endonuclease is a mutant made by a process comprising:

isolating a region of a genome from *P. haemolytica*;

introducing a mutation into said region to form a mutated DNA region;

methyating said mutated DNA region with a methylating enzyme which inhibits endonuclease cleavage at a recognition sequence selected from the group consisting of 5'-GATGC-3' and 5'-GCATC-3', to form methylated DNA;

introducing said methylated DNA into a *P. haemolytica* cell to form transformants; and

screening said transformants for those which have said mutation in said region on chromosomal DNA of said *P. haemolytica* cell.

5. A *P. haemolytica* mutant made by the process of claim 1.

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L4: Entry 9 of 18

File: USPT

Dec 15, 1998

US-PAT-NO: 5849305

DOCUMENT-IDENTIFIER: US 5849305 A

TITLE: Construction of Pasteurella haemolytica vaccines

DATE-ISSUED: December 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Briggs; Robert E.	Boone	IA		
Tatum; Fred M.	Ames	IA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE	CODE
The United States of America as represented by the Secretary of the Department of Agriculture	Washington	DC			06	
Biotechnology Research and Development Corporation	Peoria	IL			02	

APPL-NO: 08/ 643299 [\[PALM\]](#)

DATE FILED: May 8, 1996

PARENT-CASE:

This application is a division of application Ser. No. 08/162,392, filed Dec. 6, 1993 now U.S. Pat. No. 5,587,305.

INT-CL: [06] [A01 J 21/00](#), [A01 J 25/12](#), [A21 C 3/00](#), [A21 C 11/00](#)

US-CL-ISSUED: 424/255.1; 424/93.2, 424/184.1

US-CL-CURRENT: [424/255.1](#); [424/184.1](#), [424/93.2](#)

FIELD-OF-SEARCH: 424/255.1, 424/93.2, 424/184.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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ISSUE-DATE

PATENTEE-NAME

US-CL

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<input type="checkbox"/>	<u>4346074</u>	August 1982	Gilmour et al.	424/203.1
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<input type="checkbox"/>	<u>5165924</u>	November 1992	Shewen et al.	424/236.1
<input type="checkbox"/>	<u>5210035</u>	May 1993	Stocker	435/235.1
<input type="checkbox"/>	<u>5238823</u>	August 1993	Potter et al.	435/69.52
<input type="checkbox"/>	<u>5273889</u>	December 1993	Potter et al.	435/69.51
<input type="checkbox"/>	<u>5389368</u>	February 1995	Curtiss, III	424/93.2
<input type="checkbox"/>	<u>5424065</u>	June 1995	Curtiss, III	424/93.2
<input type="checkbox"/>	<u>5468485</u>	November 1995	Curtiss, III	424/184.1
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ART-UNIT: 161

PRIMARY-EXAMINER: Housel; James C.

ASSISTANT-EXAMINER: Portner; Ginny Allen

ATTY-AGENT-FIRM: Banner & Witcoff, Ltd.

ABSTRACT:

Methylation of DNA can be a critical step in the introduction of DNA into *P. haemolytica*. A methyltransferase has been isolated and molecularly cloned for this purpose. Use of the methyltransferase has allowed construction of defined, attenuated mutants for use as vaccines to protect cattle.

4 Claims, 7 Drawing figures

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☐ 1. [20040033586](#). 03 Apr 03. 19 Feb 04. Attenuated gram negative bacteria. Crooke, Helen Rachel, et al. 435/252.3; C12N001/20.

☐ 2. [6573093](#). 19 Oct 01; 03 Jun 03. Temperature sensitive plasmids of *P. haemolytica*. Briggs; Robert E., et al. 435/320.1; 424/255.1 435/471 [536/23.7](#). C12N015/00.

☐ 3. [RE38028](#). 21 Nov 00; 11 Mar 03. Molecular genetic construction of vaccine strains of *pasteurellaceae*. Briggs; Robert E., et al. 435/476; 435/243 435/252.1 435/252.3 435/320.1 435/440 435/471 435/477 435/69.1 536/23.1. C12N001/00 C12N001/21 C12N015/00 C12Q001/68.

☐ 4. [6495145](#). 19 Oct 01; 17 Dec 02. LktA deletion mutant of *P. haemolytica*. Briggs; Robert E., et al. 424/255.1; 424/234.1 424/93.4 426/2 426/89 435/455 435/69.1. A61K039/102.

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☐ 6. [6350454](#). 08 Oct 99; 26 Feb 02. Attenuated *Pasteurella piscicida* vaccine for fish. Thune; Ronald L.. 424/200.1; 424/184.1 424/201.1 424/203.1 424/234.1 424/235.1 424/255.1 424/827 424/93.4. A61K039/02 A61K039/102 A61K039/00 A61K039/295 A01N063/00.

☐ 7. [6331303](#). 25 Sep 98; 18 Dec 01. LKTA deletion mutant of *P. haemolytica*. Briggs; Robert E., et al. 424/255.1; 424/234.1 435/252.3 435/471 435/69.1. A61K039/102.

☐ 8. [6010705](#). 11 Apr 97; 04 Jan 00. Attenuated, invasive vaccines against fish pathogens. Thune; Ronald L., et al. 424/234.1; 424/184.1 424/200.1 424/235.1 424/827 424/93.1 424/93.2 424/93.4 424/93.48. A61K039/02 A61K039/00 A01N063/00.

☐ 9. [5849305](#). 08 May 96; 15 Dec 98. Construction of *Pasteurella haemolytica* vaccines. Briggs; Robert E., et al. 424/255.1; 424/184.1 424/93.2. A01J021/00 A01J025/12 A21C003/00 A21C011/00.

☐ 10. [5840556](#). 19 Dec 96; 24 Nov 98. Molecular genetic construction of vaccine strains of *pasteurellaceae*. Briggs; Robert E., et al. 435/473; 435/243 435/252.1 435/252.3 435/320.1 435/476 435/6 435/69.1 536/23.1. C12N001/00 C12N001/21 C12N015/00 C12Q001/68.

☐ 11. [5824525](#). 08 May 96; 20 Oct 98. Construction of *Pasteurella haemolytica* vaccines. Briggs; Robert E., et al. 435/6; 435/252.1 435/252.3 435/441 435/476. C12N001/21.

☐ 12. [5733780](#). 08 May 96; 31 Mar 98. Construction of *Pasteurella haemolytica* vaccines. Briggs; Robert E., et al. 435/320.1; C12N015/74 C12N015/00.

☐ 13. [5693777](#). 08 May 96; 02 Dec 97. DNA encoding *pasteurella haemolytica* *PhaI* restriction endonuclease and methyltransferase. Briggs; Robert E., et al. 536/23.2; 435/196 536/23.7. C07H021/04 C12N009/16.

☐ 14. [5683900](#). 08 May 96; 04 Nov 97. *Pasteurella haemolytica* *PhaI* restriction endonuclease and methyltransferase. Briggs; Robert E., et al. 435/196; 530/300 530/350. C12N009/16.

☐ 15. [5587305](#). 06 Dec 93; 24 Dec 96. *Pasteurella haemolytica* transformants. Briggs; Robert E., et al. 435/477; 424/93.2 435/252.1 435/252.3. C12N015/09 C12N015/63.

☐ 16. [EP001149587A2](#). 06 Dec 94. 31 Oct 01. Construction of *Pasteurella haemolytica* vaccines. BRIGGS, ROBERT E, et al. A61K039/102;.

☐ 17. [WO009846725A2](#). 09 Apr 98. 22 Oct 98. ATTENUATED, INVASIVE VACCINES AGAINST FISH PATHOGENS. THUNE, RONALD L, et al. C12N001/21; A61K039/02 A61K039/295 A61K039/102.

☐ 18. [EP 733114B](#). Prodn. of attenuated *aroA* mutants of *Pasteurella haemolytica* by DNA methylation - useful in vaccines for protection of cattle against *P. haemolytica* infection. BRIGGS, R E, et al. A01J021/00 A01J025/12 A21C003/00 A21C011/00 A61K039/102 C07H021/04 C12N001/21 C12N009/10 C12N009/16 C12N009/22 C12N015/00 C12N015/09 C12N015/54 C12N015/55 C12N015/63 C12N015/74.

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Terms	Documents
L3 and (aro or aroa or aro-a or aromatic\$)	18

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First Hit

L3: Entry 1 of 122

File: PGPB

Feb 19, 2004

PGPUB-DOCUMENT-NUMBER: 20040033586
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040033586 A1

TITLE: Attenuated gram negative bacteria

PUBLICATION-DATE: February 19, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Crooke, Helen Rachel	Winnersh Triangle		GB	
Shea, Jacqueline Elizabeth	Winnersh Triangle		GB	
Feldman, Robert Graham	Winnersh Triangle		GB	
Goutebroze, Sylvain Gabriel	Lyon		FR	
Le Gros, Francois-Xavier	Saint Genis Laval		FR	

APPL-NO: 10/ 406686 [PALM]
DATE FILED: April 3, 2003

RELATED-US-APPL-DATA:

Application is a non-provisional-of-provisional application 60/370282, filed April 5, 2002,

INT-CL: [07] C12 N 1/20

US-CL-PUBLISHED: 435/252.3

US-CL-CURRENT: 435/252.3

ABSTRACT:

Disclosed and claimed are a mutant of a gram negative bacterium, wherein said bacterium has at least one mutation in a nucleotide sequence which codes for a polypeptide having an identity which is equal or more than 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% with an amino acid sequence coded by a nucleotide sequence selected from the group consisting of nucleotide sequences identified SEQ ID NO: 2, 6, 9, 12, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 75, 78, 81, 84, 87, 90, 93; said mutation resulting in attenuated virulence of the bacterium. Immunogenic compositions and vaccines containing such a mutant are also disclosed and claimed.

RELATED APPLICATIONS/INCORPORATION BY REFERENCE

[0001] This application claims priority from U.S. provisional application Serial No. 60/370,282, filed on Apr. 5, 2002, incorporated herein by reference. The foregoing application, and all documents cited therein or during its prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any

manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

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L4: Entry 5 of 18

File: USPT

Jun 25, 2002

DOCUMENT-IDENTIFIER: US 6410021 B1

**** See image for Certificate of Correction ****TITLE: Vaccines of pasteurellaceae mutants and vaccination methodAbstract Text (1):

A live vaccine of recombinant mutants of a member of the family Pasteurellaceae lacking a rib gene necessary for production of riboflavin as well as a method of vaccination therewith is described. The vaccine is effective against members of the family Pasteurellaceae.

Brief Summary Text (6):

A variety of mutations in biosynthetic pathways are known to be attenuating in other organisms. Lesions in aro (Hoiseth S. K. and B. A. D. Stocker. 1981. Aromatic-dependent Salmonella typhimurium are non-virulent and effective as live vaccines. Nature (london). 291: 238-239) (Homchampa, P., R. A. Strugnell and B. Adler. 1992. Molecular analysis of the aroA gene of Pasteurella multocida and vaccine potential of a constructed aroA mutant. Mol. Microbiol. 6: 3585-3593) (Homchampa, P., R. A. Strugnell and B. Adler. 1994. Construction and vaccine potential of an aroA mutant of Pasteurella haemolytica. Vet. Microbiol. 42:35-44) (Karnell, A., P. D. Cam, N. Verma and A. A. Lindberg. 1993. AroD deleteion attenuates Shigella flexneri strain 2457T and makes it a safe and efficacious oral vaccine in monkeys. Vaccine 8:830-836.) (Lindberg, A. A., A. Karnell, B. A. D. Stocker, S. Katakura, H. Sweiha and F. P. Reinholt. 1988. Development of an auxotrophic oral live Shigella flexneri vaccine. Vaccine 6:146-150) (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Vaughan, L. M., P. R. Smith, and T. J. Foster. 1993. An aromatic-dependent mutant of the fish pathogen Aeromonas salmonicida is attenuated in fish and is effective as a live vaccine against the Salmonid disease furunculosis. Infect. Immun. 61:2172-2181), pur (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Sigwart, D. F., B. A. D. Stocker, and J. D. Clements. 1989. Effect of a purA mutation on the efficacy of Salmonella live vaccine vectors. Infect. Immun. 57:1858-1861), and thy (Ahmed, Z. U., M. R. Sarker, and D. A. Sack. 1990. Protection of adult rabbits and monkeys from lethal shigellosis by oral immunization with a thymine-requiring and temperature-sensitive mutant of Shigella flexneri Y. Vaccine. 8:153-158) loci, which affect the biosynthesis of aromatic amino acids, purines, and thymine, respectively, are attenuating because they eliminate the ability of the bacterium to synthesize critical compounds that are not readily available within mammalian hosts. For example, aro mutants of Salmonella and Shigella species have been shown to be attenuated in their natural hosts (Hoiseth S. K. and B. A. D. Stocker. 1981. Aromatic-dependent Salmonella typhimurium are non-virulent and effective as live vaccines. Nature (london). 291: 238-239) (Homchampa, P., R. A. Strugnell and B. Adler. 1992. Molecular analysis of the aroA gene of Pasteurella multocida and vaccine potential of a constructed aroA mutant. Mol. Microbiol. 6: 3585-3593) (Homchampa, P., R. A. Strugnell and B. Adler. 1994. Construction and vaccine potential of an aroA mutant of Pasteurella

haemolytica. Vet. Microbiol. 42:35-44) (Karnell, A., P. D. Cam, N. Verma and A. A. Lindberg. 1993. AroD deletion attenuates Shigella flexneri strain 2457T and makes it a safe and efficacious oral vaccine in monkeys. Vaccine 8:830-836) (Lindberg, A. A., A. Karnell, B. A. D. Stocker, S. Katakura, H. Sweiha and F. P. Reinholt. 1988. Development of an auxotrophic oral live Shigella flexneri vaccine. Vaccine 6:146-150) (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423). Lesions that affect the biosynthesis of LPS (Collins, L. V., S. Attridge, and J. Hackett. 1991. Mutations at rfc or pmi attenuate Salmonella typhimurium virulence for mice. Infect. Immun. 59:1079-1085) (Nnalue, N. A., and B. A. D. Stocker. 1987. Tests of the virulence and live-vaccine efficacy of auxotrophic and gale derivatives of Salmonella cholerasuis. Infect. Immun. 55:955-962) and of cyclic AMP (Kelly, S. M., B. A. Bosecker and R. Curtiss III. 1992. Characterization and protective properties of attenuated mutants of Salmonella cholerasuis. Infect. Immun. 60:4881-4890) (Tacket, C. I., D. M. Hone, R. Curtiss III, S. M. Kelly, G. Losonsky, L. Guers. A. M. Harris, R. Edelman. M. M. Levine. 1992. Comparison of the safety and immunogenicity of .DELTA.aroC .DELTA.aroD and .DELTA.cya.DELTA.crp Salmonella typhi strains in adult volunteers. Infect. Immun. 60:536-541) have also been shown to be attenuating in Salmonella species. It is important to note that not all attenuating mutations are good vaccine candidates in different organisms because some attenuating mutations result in poor persistence and immunogenicity (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Sigwart, D. F., B. A. D. Stocker, and J. D. Clements. 1989. Effect of a purA mutation on the efficacy of Salmonella live vaccine vectors. Infect. Immun. 57:1858-1861).

Detailed Description Text (87):

A second method to produce live avirulent vaccines is to knock out genes in biosynthetic pathways known to be critical for survival in vivo. For example, the availability of compounds such as purines and aromatic amino acids is limited in mammalian hosts. Bacterial pathogens must be able to synthesize these compound themselves, or scavenge them from host tissues. Mutations in the biosynthetic pathways for purines and aromatic amino acids have been used to construct bacterial mutants that can not survive long in vivo, and thus have potential for use as attenuated vaccines. Much of the current research on genetically engineered live avirulent vaccines has been done with members of the genus Salmonella. These studies show that purA mutants are avirulent but poorly immunogenic (O'Callaghan et al, 1988), while mutations in the chorismate pathway, including aroA, aroC, and aroD, are attenuated and can be effective as live oral vaccines (Doggett & Curtiss, 1992; Tacket et al, 1992). In addition, Salmonella strains carrying cya and crp mutations, which produce mutants that lack the enzyme adenylate cyclase and the cyclic AMP receptor protein, which are required for the expression of numerous critical genes in bacteria, have been shown to be both avirulent and immunogenic (Doggett & Curtiss, 1992; Tacket et al, 1992; Kelly et al, 1992).

Detailed Description Text (142):

49. O'Callaghan, D., et al. 1988. Characterization of aromatic and purine-dependent Salmonella typhimurium: attenuation, persistence, and ability to induce protective immunity in Balb/c mice . Infect. Immun. 56: 419-423.

CLAIMS:

1. A live vaccine against members of the family of Pasteurellaceae comprising a recombinant mutant of a member of the family of Pasteurellaceae lacking a rib gene necessary for the production of riboflavin in a pharmaceutically acceptable carrier.

4. A method of vaccinating a mammal in need thereof comprising administering to the mammal an effective vaccinating amount of a live vaccine comprising a recombinant mutant of a member of the family of Pasteurellaceae lacking a rib gene necessary for the production of riboflavin in a pharmaceutically acceptable carrier.

5. A method of stimulating the immune system of a mammal in need thereof comprising the steps of:

(a) providing a recombinant Pasteurellaceae mutant having an inactivating mutation in one or more rib genes necessary for the production of riboflavin; and

(b) administering an effective immunogenic amount of the recombinant Pasteurellaceae mutant in a pharmaceutically acceptable carrier to a mammal in need thereof, thereby causing an antigenic response thereto, which stimulates the immune system in the mammal.

6. A method of inducing protective immunity in a mammal in need thereof against disease caused by Family Pasteurellaceae comprising the step of administering to the mammal an effective amount of a recombinant Pasteurellaceae mutant having an inactivating mutation in one or more rib genes necessary for the production of riboflavin in a pharmaceutically acceptable carrier such that the mutant causes protective immunity in the mammal against Pasteurellaceae.

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L4: Entry 5 of 18

File: USPT

Jun 25, 2002

DOCUMENT-IDENTIFIER: US 6410021 B1

**** See image for Certificate of Correction ****TITLE: Vaccines of pasteurellaceae mutants and vaccination methodAbstract Text (1):

A live vaccine of recombinant mutants of a member of the family Pasteurellaceae lacking a rib gene necessary for production of riboflavin as well as a method of vaccination therewith is described. The vaccine is effective against members of the family Pasteurellaceae.

Brief Summary Text (6):

A variety of mutations in biosynthetic pathways are known to be attenuating in other organisms. Lesions in aro (Hoiseth S. K. and B. A. D. Stocker. 1981. Aromatic-dependent Salmonella typhimurium are non-virulent and effective as live vaccines. Nature (london). 291: 238-239) (Homchampa, P., R. A. Strugnell and B. Adler. 1992. Molecular analysis of the aroA gene of Pasteurella multocida and vaccine potential of a constructed aroA mutant. Mol. Microbiol. 6: 3585-3593) (Homchampa, P., R. A. Strugnell and B. Adler. 1994. Construction and vaccine potential of an aroA mutant of Pasteurella haemolytica. Vet. Microbiol. 42:35-44) (Karnell, A., P. D. Cam, N. Verma and A. A. Lindberg. 1993. AroD deletion attenuates Shigella flexneri strain 2457T and makes it a safe and efficacious oral vaccine in monkeys. Vaccine 8:830-836.) (Lindberg, A. A., A. Karnell, B. A. D. Stocker, S. Katakura, H. Sweiha and F. P. Reinholt. 1988. Development of an auxotrophic oral live Shigella flexneri vaccine. Vaccine 6:146-150) (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Vaughan, L. M., P. R. Smith, and T. J. Foster. 1993. An aromatic-dependent mutant of the fish pathogen Aeromonas salmonicida is attenuated in fish and is effective as a live vaccine against the Salmonid disease furunculosis. Infect. Immun. 61:2172-2181), pur (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Sigwart, D. F., B. A. D. Stocker, and J. D. Clements. 1989. Effect of a purA mutation on the efficacy of Salmonella live vaccine vectors. Infect. Immun. 57:1858-1861), and thy (Ahmed, Z. U., M. R. Sarker, and D. A. Sack. 1990. Protection of adult rabbits and monkeys from lethal shigellosis by oral immunization with a thymine-requiring and temperature-sensitive mutant of Shigella flexneri Y. Vaccine. 8:153-158) loci, which affect the biosynthesis of aromatic amino acids, purines, and thymine, respectively, are attenuating because they eliminate the ability of the bacterium to synthesize critical compounds that are not readily available within mammalian hosts. For example, aro mutants of Salmonella and Shigella species have been shown to be attenuated in their natural hosts (Hoiseth S. K. and B. A. D. Stocker. 1981. Aromatic-dependent Salmonella typhimurium are non-virulent and effective as live vaccines. Nature (london). 291: 238-239) (Homchampa, P., R. A. Strugnell and B. Adler. 1992. Molecular analysis of the aroA gene of Pasteurella multocida and vaccine potential of a constructed aroA mutant. Mol. Microbiol. 6: 3585-3593) (Homchampa, P., R. A. Strugnell and B. Adler. 1994. Construction and vaccine potential of an aroA mutant of Pasteurella

haemolytica. Vet. Microbiol. 42:35-44) (Karnell, A., P. D. Cam, N. Verma and A. A. Lindberg. 1993. AroD deletion attenuates Shigella flexneri strain 2457T and makes it a safe and efficacious oral vaccine in monkeys. Vaccine 8:830-836) (Lindberg, A. A., A. Karnell, B. A. D. Stocker, S. Katakura, H. Sweiha and F. P. Reinholt. 1988. Development of an auxotrophic oral live Shigella flexneri vaccine. Vaccine 6:146-150) (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423). Lesions that affect the biosynthesis of LPS (Collins, L. V., S. Attridge, and J. Hackett. 1991. Mutations at rfc or pmi attenuate Salmonella typhimurium virulence for mice. Infect. Immun. 59:1079-1085) (Nnalue, N. A., and B. A. D. Stocker. 1987. Tests of the virulence and live-vaccine efficacy of auxotrophic and gale derivatives of Salmonella choleraesuis. Infect. Immun. 55:955-962) and of cyclic AMP (Kelly, S. M., B. A. Bosecker and R. Curtiss III. 1992. Characterization and protective properties of attenuated mutants of Salmonella choleraesuis. Infect. Immun. 60:4881-4890) (Tacket, C. I., D. M. Hone, R. Curtiss III, S. M. Kelly, G. Losonsky, L. Guers. A. M. Harris, R. Edelman. M. M. Levine. 1992. Comparison of the safety and immunogenicity of .DELTA.aroC .DELTA.aroD and .DELTA.cya.DELTA.crp Salmonella typhi strains in adult volunteers. Infect. Immun. 60:536-541) have also been shown to be attenuating in Salmonella species. It is important to note that not all attenuating mutations are good vaccine candidates in different organisms because some attenuating mutations result in poor persistence and immunogenicity (O'Callaghan, D. D. Maskell, F. Y. Lieu, C. S. F. Easmon and G. Dougan. 1988. Characterization of aromatic and purine dependent Salmonella typhimurium: attenuation, persistence and ability to induce protective immunity in BALB/c mice. Infect. Immun. 56:419-423) (Sigwart, D. F., B. A. D. Stocker, and J. D. Clements. 1989. Effect of a purA mutation on the efficacy of Salmonella live vaccine vectors. Infect. Immun. 57:1858-1861).

Detailed Description Text (87):

A second method to produce live avirulent vaccines is to knock out genes in biosynthetic pathways known to be critical for survival in vivo. For example, the availability of compounds such as purines and aromatic amino acids is limited in mammalian hosts. Bacterial pathogens must be able to synthesize these compound themselves, or scavenge them from host tissues. Mutations in the biosynthetic pathways for purines and aromatic amino acids have been used to construct bacterial mutants that can not survive long in vivo, and thus have potential for use as attenuated vaccines. Much of the current research on genetically engineered live avirulent vaccines has been done with members of the genus Salmonella. These studies show that purA mutants are avirulent but poorly immunogenic (O'Callaghan et al, 1988), while mutations in the chorismate pathway, including aroA, aroC, and aroD, are attenuated and can be effective as live oral vaccines (Doggett & Curtiss, 1992; Tacket et al, 1992). In addition, Salmonella strains carrying cya and crp mutations, which produce mutants that lack the enzyme adenylate cyclase and the cyclic AMP receptor protein, which are required for the expression of numerous critical genes in bacteria, have been shown to be both avirulent and immunogenic (Doggett & Curtiss, 1992; Tacket et al, 1992; Kelly et al, 1992).

Detailed Description Text (142):

49. O'Callaghan, D., et al. 1988. Characterization of aromatic and purine-dependent Salmonella typhimurium: attenuation, persistence, and ability to induce protective immunity in Balb/c mice . Infect. Immun. 56: 419-423.

CLAIMS:

1. A live vaccine against members of the family of Pasteurellaceae comprising a recombinant mutant of a member of the family of Pasteurellaceae lacking a rib gene necessary for the production of riboflavin in a pharmaceutically acceptable carrier.

4. A method of vaccinating a mammal in need thereof comprising administering to the mammal an effective vaccinating amount of a live vaccine comprising a recombinant mutant of a member of the family of Pasteurellaceae lacking a rib gene necessary for the production of riboflavin in a pharmaceutically acceptable carrier.

5. A method of stimulating the immune system of a mammal in need thereof comprising the steps of:

(a) providing a recombinant Pasteurellaceae mutant having an inactivating mutation in one or more rib genes necessary for the production of riboflavin; and

(b) administering an effective immunogenic amount of the recombinant Pasteurellaceae mutant in a pharmaceutically acceptable carrier to a mammal in need thereof, thereby causing an antigenic response thereto, which stimulates the immune system in the mammal.

6. A method of inducing protective immunity in a mammal in need thereof against disease caused by Family Pasteurellaceae comprising the step of administering to the mammal an effective amount of a recombinant Pasteurellaceae mutant having an inactivating mutation in one or more rib genes necessary for the production of riboflavin in a pharmaceutically acceptable carrier such that the mutant causes protective immunity in the mammal against Pasteurellaceae.

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Construction and vaccine potential of an aroA mutant of *Pasteurella haemolytica*.

Homchampa P, Strugnell RA, Adler B.

Department of Microbiology, Monash University, Clayton, Melbourne, Vic., Australia.

The aroA gene, encoding 5-enolpyruvylshikimate 3-phosphate synthase, from *Pasteurella haemolytica* biotype A, serotype 1 was cloned by complementation of the aroA mutation in *Escherichia coli* strain AB2829 after electroporation with a DNA library constructed in pUC18. The cloned *P. haemolytica* aroA gene was inactivated by insertion of a kanamycin resistance gene and reintroduced by allelic exchange into the chromosome of the parental *P. haemolytica* using PbluescriptII SK+. The *P. haemolytica* aroA mutant was highly attenuated in a mouse septicaemic model. Mice immunized intraperitoneally with two doses of live *P. haemolytica* aroA mutant were protected against a lethal parental strain challenge.

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(Homchampa, P., R. A. Strugnell and B. Adler. 1994. Construction and vaccine potential of an aroA mutant of Pasteurella haemolytica. Vet. Microbiol. 42:35-44) (Karnell, A., P. D. Cam, N. Verma and A. A. Lindberg. 1993.

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